REMARKS

Claims 1-3, 7-15, 19-24, 28-30 are pending. Claims 19 and 29 have been canceled. Claims 1, 22-24, 28, and 30 have been amended.

The Office Action states that claims 1-3, 7, 13, 14, 19-24, and 28-30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over United States Patent No. 5,998,457 to Kaddurah-Daouk ("Kaddurah") in view of United States Patent No. 4,772,591 to Meisner ("Meisner"), United States Patent No. 5,888,553 to Grant *et al.* ("Grant"), United States Patent No. 5,756,496 to Beale *et al.* ("Beale '496") and United States Patent No. 5,716,926 to Beale *et al.* ("Beale 926").

As amended herein, claim 1 recites:

> [a] method of treating at least one bone or cartilage condition which comprises administering to an animal a therapeutically effective amount of an agent comprising creatine, or an analogue or pharmaceutically acceptable salt thereof, to treat bone or cartilage condition s, wherein the agent is essentially free of one or more of dihydrotriazine; dicyano-diamide; or creatinine.

As amended herein, claim 22 recites:

> A method of promoting growth and mineralization of bone or cartilage cells and tissues which comprises administering to a subject in need of such treatment a therapeutically effective amount of an agent comprising creatine pyruvate or an analogue thereof, to promote growth and mineralization of bone or cartilage therein, wherein the agent is essentially free of one or more of dihydrotriazine; dicyano-diamide; or creatinine.

It is submitted that no combination of the cited references discloses, suggests, or teaches a method comprising administration of a composition essentially free of one or more of dihydrotriazine; dicyano-diamide; or creatinine, as set forth in claims 1 and 22, as amended. Accordingly, claims 1 and 22 are understood to be patentable in view of the cited art.

It is also submitted that the Office Action does not set forth a prima facie case of obviousness with respect to claims 23, 24, 28, and 30 at least because no combination of the cited references discloses, suggests, or teaches any of the methods set forth in these claims.

Neither Kaddurah, Meisner, nor Grant disclose use of pyruvate for any purpose. Beale '926 discloses use of pyruvate in treating osteoporosis. Beale '926 does not disclose use of creatine for any purpose. Beale '469 discloses use of pyruvate in addition to a

cortisol blocker, such as creatine, for increasing lean muscle mass or enhancing the energy level of a mammal. Beale '469, 3:58-63.

It is submitted, however, that no combination of the cited references, discloses: administration of (i) at least one of (1) creatine or an analogue thereof and (2) a pharmaceutically acceptable salt of creatine or analog thereof, and (ii) pyruvate to improve acceptance and osseous integration of bone implants (claim 23); accelerating healing in a subject having a defect in bone or cartilage tissue caused by trauma or surgery by a method comprising administering to the subject a therapeutically effective amount of (i) at least one of (1) a creatine compound or analogue thereof, (2) a pharmaceutically acceptable salt of creatine or analog thereof, and (3) a creatine kinase, and (ii) pyruvate (claim 24); treating osteoarthritis unrelated to weight gain or weight loss by a method comprising administering to an animal a therapeutically effective amount of an agent comprising creatine pyruvate or an analogue thereof (claim 28); or treating at least one of osteoarthritis and periodontitis by a method comprising administering to an animal a therapeutically effective amount of an agent comprising creatine pyruvate or an analogue thereof. Thus, a prima facie case of obviousness has not been set forth with respect to any of claims 23, 24, 28, and 30, as amended. *See In re Royka*, 490 F.2d 981, (CCPA 1974); M.P.E.P., 2143.03.

Moreover, Applicants submit there is nothing in the cited references that would have motivated one to even attempt their combination to achieve the inventions of any of claims 23, 24, 28, and 30. The Office Action does not identify a proper motivation to combine. In an attempt to address this weakness, the Office Action states that:

> Grant et al. teaches that the excess of cortisol is known to be a cause of osteoporosis, tissue degeneration . . .
>
> Beale ('469) teaches creatine pyruvate (pyruvyl-creatine) is particularly useful as cortisol antagonist or cortisol blocker for prevent the catabolic activity of cortisol. See column 1, lines 7-18, 54-60; column 3, lines 46-63.

It is respectfully, submitted, however, that one would not have understood Beale '469 to disclose that pyruvate is useful as a cortisol antagonist or cortisol blocker. For example, Beale '469 discloses "a composition which comprises pyruvate and/or derivatives of pyruvate and an anti-cortisol or cortisol blocker compound." (emphasis added). Beale '469, 1:12-14. Elsewhere, Beale '469 discloses that "[c]reatine monohydrate is an additional cortisol blocker that, when combined with pyruvate, produces a synergistic effect in increasing the lean body mass of a mammal." *Id.*, 3:58-63. Thus, it is submitted that one

would only have understood Beale '469 to disclose use of pyruvate in addition to a cortisol blocker for increasing lean muscle mass or enhancing the energy level of a mammal. *Id.*, 3:58-63. At least because Beale '469 fails to disclose pyruvate to have anti-cortisol activity, Grant provides no motivation to combine Beale '469 with other cited references (nor has Applicant found motivation elsewhere in the cited references).

Moreover, Beale '469's disclosure itself of pyruvate in a composition for increasing lean muscle mass or enhancing energy levels does not motivate for use of pyruvate as claimed for improving acceptance and osseous integration of bone implants (claim 23); accelerating healing in a subject having a defect in bone or cartilage tissue caused by trauma or surgery (claim 24); treating osteoarthritis unrelated to weight gain or weight loss (claim 28), or treating at least one of osteoarthritis and periodontitis (claim 30).

The remaining references (whether alone or in any combination including Beale '469) also lack motivation for their combination. Beale '926's disclosure of pyruvate for treating osteoporosis, would not have motivated one to event attempt the claimed improving acceptance and osseous integration of bone implants (claim 23); accelerating healing in a subject having a defect in bone or cartilage tissue caused by trauma or surgery (claim 24); treating osteoarthritis unrelated to weight gain or weight loss (claim 28), or treating at least one of osteoarthritis and periodontitis (claim 30). Kadduh, Grant, and Meisner neither disclose pyruvate for any purpose nor motivate that they be modified to include pyruvate.

In view of the foregoing amendments and remarks, it is believed that the rejections in the Office Action have been overcome. Insofar as the foregoing comments with respect to the independent claims are equally applicable to their respective dependent claims, the rejections of the dependent claims are also believed to have been overcome for this reason as well as others presented herein. Applicants respectfully submit that the prior art cited in this case taken individually or in combination neither discloses nor suggests the inventions recited in independent claims 1, 22-24, 28, and 30. Thus, the claims as presented and amended herein are submitted to be in condition for allowance.

No fee is believed due for this submission. Should any fees be required, however, please charge such fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

If the Examiner wishes to discuss this case, then Applicants respectfully request a personal or telephonic interview to discuss any remaining issues and expedite the allowance of the application.

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Respectfully submitted,

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Enclosure

APPENDIX A

Marked up copy of pending claims.

1. (Amended) A method of treating at least one bone or cartilage condition which comprises administering to an animal a therapeutically effective amount of an agent comprising creatine, or an analogue or pharmaceutically acceptable salt thereof, to treat bone or cartilage conditions, wherein the agent is essentially free of one or more of dihydrotriazine; dicyano-diamide; or creatinine.

2. The method of claim 1, wherein the animal is a mammal and the condition comprises a bone or cartilage disease, a bone fracture or defect, or a degenerative disease of cartilage.

3. The method of claim 2, wherein the mammal is a human and the disease comprises osteoporosis, osteoarthritis, or periodontitis.

7. The method of claim 1, wherein the creatine, or analogue or pharmaceutically acceptable salt thereof, comprises creatine, creatine phosphate, creatine pyruvate, cyclocreatine, homocreatine, or homocyclocreatine.

13. The method of claim 1, wherein the bone comprises cells comprising osteoblasts, periosteal cell, stromal bone marrow cells, satellite cells of muscle tissue, or mesenchymal stem cells, or a combination thereof.

14. The method of claim 1, wherein the cartilage comprises cells comprising chondroblasts or mesenchymal stem cells.

19. (Canceled)

20. The method of claim 1, wherein the agent is administered to a human patient in an amount of 1.4 to 285 mg per day.

21. The method of claim 1, wherein the creatine analogue has the general formula:

Z_1- - -C(- - -Z_2)- - -X-A-Y

and pharmaceutically acceptable salts thereof, wherein:

Y is selected from: -CO_2H, -NI-OH, -NO_2, -SO_3H, -C(=O)$NHSO_2J$, and -P(=O) (OH) (OJ), wherein J is selected from: hydrogen, C_1-C_6 straight chain alkyl, C_3-C_6 branched alkyl, C_2-C_6 straight alkenyl, C_3-C_6 branched alkenyl and aryl;

A is selected from: C, CH, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and C_1-C_5 alkoyl chain, each having 0-2 substituents which are selected independently from:

K, where K is selected from: C_1-C_6 straight alkyl, C_2-C_6 straight alkenyl, C_1-C_6 straight alkoyl, 3-6 branched alkyl, C_3-C_6 branched alkenyl, C_4-C_6 branched alkoyl, K having 0-2 substituents independently selected from: bromo, chloro, epoxy and acetoxy;

an aryl group selected from: a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from: -CH_2L and -$COCH_2L$, wherein L is independently selected from: bromo, chloro, epoxy and acetoxy; and

-NH-M, wherein M is selected from: hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkoyl, C_3-C_4 branched alkyl, C_3-C_4 branched alkenyl, and C_4-C_6 branched alkoyl;

X is selected from: NR_1, CHR_1, CR_1, O and 5,

wherein R_1 is selected from:

hydrogen,

K where K is defined above; and

an aryl group selected from: a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from: -CH_2L and -$COCH_2L$ where L is defined above;

a C_5-C_9 Alpha-amino-omega-methyl-omega-adenosyl carboxylic acid attached via the omega-methyl carbon;

a C_5-C_9 Alpha-amino-omega-aza-omega-methyl-omega -adenosylcarboxylic acid attached via the omega-methyl carbon; and

a C_5-C_9 Alpha-amino-omega-thia-omega-methyl-omegaadenosylcarboxylic acid wherein A and X are connected by a single or double bond;

Z_1 and Z_2 are chosen independently from: =O, -NHR_2, -CH_2R_2, -NR_2OH; wherein, Z_1 and Z_2 may not both be =O and wherein R_2 is selected from:

hydrogen;

K, where K is defined above;

an aryl group selected from: a 1-2 ring carbocycle and a 1-2 ring heterocycle, wherein the aryl group contains 0-2 substituents independently selected from: -CH_2L and -$COCH_2L$ where L is as defined above;

a C_4-C_8 Alpha-amino-carboxylic acid attached via the omega - carbon;

B, wherein B is selected from: -CO_2H, -NHOH, NO_2, -SO_3H, -C(=O)$NHSO_2J$ and -P(=O) (OH) (OJ), wherein J is as defined above:

D-E, wherein D is selected from: C_1-C_3 straight chain alkyl, C_3 branched alkyl, C_2-C_3 straight alkenyl, C_3 branched alkenyl, C_1-C_3 straight alkoyl, and aryl; and E is selected from: -$(PO_3)_n$NMP, where n is 0-2 and NMP is a ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; -$[P(=0)(OCH_3)(O)]_m$-Q, wherein m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; -$[P(=O)(OH)(CH_2)]_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose of the aromatic ring of the base; and an aryl group containing 0-3

substituents chosen independently from: Cl, Br, epoxy, acetoxy, -OG, -C(=O)G, and -CO_2G, where G is independently selected from: C_1-C_6 straight alkyl, C_2-C_6 straight alkenyl, C_1-C_6 straight alkoyl, C_3-C_6 branched alkyl, C_1-C_6 branched alkenyl, C_4-C_6 branched alkoyl; wherein E may be attached at any point to D, and if D is alkyl or alkenyl, D may be connected at either or both ends by an amide linkage; and

E, wherein E is as defined above,

provided that:

when E is aryl, B may be connected by an amide linkage;

if R_1 and at least one R_2 group are present, R_1 may be connected by a single or double bond to an R_2 group to form a cycle of 5 to 7 members;

if two R_2 groups are present, they may be connected by a single or double bond to form a cycle of 5 to 7 members; and

if R_1 is present and or Z_2 is selected from -NHR_2, -CH_2R_2 and -NR_2OH, then R_1 may be connected by a single or double bond to the carbon or nitrogen of either Z_1 or to form a cycle of 4 to 7 members.

22. (Twice Amended) A method of promoting growth and mineralization of bone or cartilage cells and tissues which comprises administering to a subject in need of such treatment a therapeutically effective amount of an agent comprising creatine pyruvate[,] or an analogue [or pharmaceutically acceptable salt] thereof, to promote growth and mineralization of bone or cartilage therein, wherein the agent is essentially free of one or more of dihydrotriazine; dicyano-diamide; or creatinine.

23. (Twice Amended) A method of improving acceptance and osseous integration of bone implants which comprises administering to a subject in need of such treatment a therapeutically effective amount of an agent comprising (i) at least one of (1) creatine or an analogue thereof [or] and (2) a pharmaceutically acceptable salt of creatine or analog thereof, and (ii) pyruvate to improve acceptance and osseous integration of bone implants.

24. (Amended) A method for accelerating healing in a subject having a defect in bone or cartilage tissue caused by trauma or surgery, which method comprises administering to the subject a therapeutically effective amount of (i) at least one of (1) a creatine compound or analogue thereof, [or] (2) a pharmaceutically acceptable salt of creatine or analog thereof, and [or] (3) a creatine kinase, and (ii) pyruvate.

28. (Amended) A method of treating [at least one of (1) osteoporosis unrelated to weight gain or weight loss and (2)] osteoarthritis unrelated to weight gain or weight loss, which comprises administering to an animal a therapeutically effective amount

of an agent comprising creatine pyruvate or an analogue [or pharmaceutically acceptable salt] thereof, to treat the [at least one of (1) osteoporosis unrelated to weight gain or weight loss and (2)] osteoarthritis unrelated to weight gain or weight loss.

29. (Canceled)

30. (Amended) A method of treating at least one bone or cartilage condition which comprises administering to an animal a therapeutically effective amount of an agent comprising creatine pyruvate or an analogue thereof, to treat at least one of [osteoporosis,] osteoarthritis[,] and periodontitis.